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Vegetable and fruit consumption and risk of renal cell carcinoma: Results from the Netherlands cohort study

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Vegetable and fruit consumption is generally inversely associated with various cancer types, including renal cell carcinoma (RCC). The Netherlands cohort study on diet and cancer (NLCS) consists of 120,852 men and women, aged 55–69 years, who filled out a self-administered questionnaire that includes 150-item food-frequency questions and additional questions on lifestyle factors, at baseline in 1986. A case-cohort approach was used. After 9.3 years of follow-up, 275 microscopically confirmed incident cases were identified. Subjects with incomplete or inconsistent dietary data were excluded, leaving 260 RCC cases for analyses on fruit consumption and 249 RCC cases for analyses on vegetable consumption. Incidence rate ratios (RR) and corresponding 95% confidence intervals (CI) were estimated using Cox proportional hazard models. RRs for exposure variables are expressed per increment of 25 g/day and are adjusted for age, sex, smoking, body mass index and history of hypertension at baseline. The RRs for vegetable consumption were further adjusted for fruit consumption and vice versa. Total vegetable and fruit consumption (RR: 1.00; 95% CI 0.97–1.02), vegetable (RR: 1.00, 95% CI 0.96–1.06) and fruit consumption (RR: 1.00; 95% CI 0.97–1.03) were not associated with RCC risk. Also, no association existed for botanical subgroups of vegetables and fruit. For 30 individual vegetables and fruits, we observed one that significantly increased RR (mandarin consumption, RR: 1.76; 95% CI 1.28–2.42), which must be regarded cautiously because of multiple testing. These results suggest the absence of an association between vegetable and/or fruit consumption and RCC risk.

Key words: renal cell carcinoma; diet; vegetable; fruit; cohort study

In general, vegetable and fruit consumption is assumed to reduce risk of various cancer types. Most reviews on renal cell carcinoma (RCC) also conclude that vegetable and fruit consumption may reduce RCC risk.[1–5] Statistically significant reduced risks for RCC have been reported for the highest tertile of vegetable and fruit consumption,[6] for vegetable and fruit consumption but restricted to men,[7] for cruciferous/dark green vegetables,[8] for vegetable and vegetable juice consumption,[9] for carrot consumption,[10] for root vegetable and banana consumption[11] and for fruit consumption.[12,13] Furthermore, 2 studies showed estimates pointing in the direction of a protective effect, but associations were not statistically significantly different from one.[14,15] Finally, 3 studies observed null associations.[16–18]

Antioxidant vitamins, fibres or enzyme inducers present in vegetable and fruits might be responsible for this preventive effect.[5] Plants rich in nitrosation inhibitors, antioxidants or enzyme inducers, *e.g.,* ascorbate and polyphenols or carotenoid-rich vegetables, garlic and cruciferous vegetables, may thus be most effective in preventing cancer.[5] The biologic plausibility that vegetable and fruit consumption reduces cancer risk is present, but reported results do not support this notion unequivocally.[6–18]

We investigated total vegetable and fruit consumption, as well as the consumption of botanical groups of vegetables and fruits and individual vegetables and fruits and RCC risk in a large cohort. For some important risk factors stratified analyses will be carried out, *e.g.,* for smoking because smoking increases oxidative stress and a more pronounced protective effect has been reported for never smokers.[12,15]

Material and methods

Netherlands Cohort Study

The Netherlands Cohort Study on diet and cancer is a large cohort study that started in September 1986. The study design has been reported in detail elsewhere.[19] Briefly, the cohort included 120,852 men and women aged 55–69 years in 1986. An elderly cohort was selected because dietary habits (and their contrasts) are stabilized, and such a cohort will yield sufficient cases for meaningful analyses within a reasonable time period.[19] The case-cohort design was used, which means that a subcohort of 5,000 men and women was randomly sampled from the cohort after baseline exposure measurement to estimate the number of person-years for the entire cohort, whereas cases were enumerated for the entire cohort.[20]

Follow-up for incident cancers and vital status

The entire cohort was followed for incident cancer by computerized record linkage with the Netherlands Cancer Registry and PALGA, a national database of pathology reports. The method of record linkage to obtain information on cancer incidence has been described previously.[21] The completeness of cancer follow-up was estimated to be more than 96%.[22] After 9.3 years of follow-up, 275 incident RCC cases have been identified.

The subcohort has been followed up for vital status information biennially by mail. The vital status of subcohort members who did not respond was completed by contacting municipal population registries. Only 2 male subcohort members were lost to follow-up after 9.3 years and were censored. Subcohort members with prevalent cancer at baseline (other than skin cancer) were excluded from analyses, leaving 4,779 subcohort members.

Questionnaire

At baseline, all cohort members completed a mailed, self-administered questionnaire on dietary habits, lifestyle, smoking, personal and family history of cancer and demographic data. The dietary section was a 150-item semiquantitative food-frequency questionnaire, which was validated against 3-day diaries completed at 3 time points during a calendar year.[23] The questionnaire concentrated on the habitual consumption of food and beverages during the year preceding the start of our study. With regard to vegetable consumption, participants were asked to report their frequency of consumption of a number of vegetables, both in summer and in winter. They could choose 1 of 6 categories, ranging from "never or less than once a month" to "3 to 7 times per week." Usual serving sizes were asked for string beans and cooked endive

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only, the mean of which served as an indicator for serving sizes of all cooked vegetables. This procedure was chosen because in a pilot study (based on an extensive dietary history with food models and photos used to estimate individual portion sizes) it was shown that serving sizes of different types of cooked vegetables were correlated within subjects.[24] To derive an individual serving size for each type of vegetable, the indicator serving size was multiplied with a type-specific factor calculated from the same pilot study data as the ratio of the means of the specific to the indicator serving sizes.[24] For tomatoes and sweet peppers, consumption was asked in pieces per week and month, respectively, during summer and winter. With regard to fruit consumption, frequencies varying from "never or less than once a month" to "6 or 7 days per week" and amounts consumed could be reported for mandarins, oranges, grapefruits, grapes, bananas, apples/pears and strawberries. Using standard portion sizes, these frequencies and amounts have been converted to consumption in grams per day. The choice of items for inclusion in the questionnaire was such that it covered almost all vegetables and fruits eaten regularly, with the exceptions of chicory, red cabbage and cucumber. Broccoli was a rarely available vegetable in 1986 and therefore not included. However, an open-ended question on other foods eaten on a regular basis was included. Participants could write down how many times per week they ate such a food and how much they were used to eating on each occasion.

According to criteria published previously,[23] subjects with incomplete or inconsistent dietary data were excluded; 260 RCC cases and 4,441 subcohort members remained for analyses on fruit consumption. In addition, we computed an error index based on the consistency of responses on vegetable questions. Questions on vegetable consumption appeared early in the questionnaire, which led some subjects to make mistakes on these particular items, whereas items appearing further along in the questionnaire were filled out without problems. When the vegetable error index exceeded a certain value, *i.e.,* more than 3 errors, subjects were excluded from analyses on vegetable consumption. Therefore, data analysis regarding vegetable consumption was based on 249 RCC cases and 4,201 subcohort members.

Data analysis

Rate ratios (RRs) were calculated for total vegetable and fruit consumption, total vegetable consumption, total fruit consumption, cooked vegetable consumption and raw vegetable consumption. RRs were also calculated for botanical groups of vegetables and fruits (composition of botanical groups is shown in Appendix I), with the exception of groups based on one main constituent (carrots, beets, tomatoes, grapes, bananas and strawberries). These were analysed in the individual vegetable and fruit analysis only. RRs were calculated per increment of 25 g/day. Also, subjects were classified into quintiles and tertiles of vegetable or fruit consumption, based on the distribution in the subcohort. Analyses for total vegetable and fruit consumption, total vegetable, and total fruit consumption have been repeated excluding the first 2 years of follow-up to evaluate whether preclinical RCC influenced results.

Based on the literature and previous analyses, considered confounders were age (continuous), sex, cigarette smoking (current smoker yes or no, number of smoking years and number of cigarettes per day), alcohol intake, body mass index (BMI), history of hypertension, physical activity, energy intake and social economic status (SES) based on education. We did not adjust for family history of RCC (present or not in a first-degree relative) because only 49 participants (4 cases and 45 subcohort members) reported a first-degree relative with RCC. Age and sex were included in all analyses. Factors that statistically significantly contributed to the model were entered in the multivariable model, leaving BMI and a history of hypertension. Smoking was also entered because some of the smoking variables to describe the smoking status satisfied this criterion as well.

TABLE I – MEAN DAILY VEGETABLE AND FRUIT CONSUMPTION AMONG RENAL CELL CARCINOMA (RCC) CASES AND SUBCOHORT MEMBERS AT BASELINE, NETHERLANDS COHORT STUDY ON DIET AND CANCER, 1986–1995

Exposure variables	Cases Mean (SD)	Subcohort Mean (SD)
Total vegetables and fruit[1]	350.5 (141.3)	362.1 (151.9)
Total vegetables[1]	190.4 (76.7)	188.4 (75.6)
Cooked vegetables[1]	152.4 (65.3)	149.3 (61.3)
Raw vegetables[1]	38.0 (23.7)	39.1 (29.6)
Legumes[1]	36.1 (25.0)	32.4 (22.1)
Brassicas[1]	32.9 (20.2)	31.7 (19.8)
Leafy vegetables, cooked[1]	21.9 (15.5)	21.3 (15.8)
Leafy vegetables, raw[1]	9.1 (7.9)	10.0 (9.0)
Allium vegetables, cooked[1]	29.6 (24.8)	29.1 (24.3)
Total fruit[2]	161.9 (112.2)	175.3 (119.4)
Citrus fruit[2]	73.0 (71.4)	77.0 (74.3)
Apples, pears[2]	81.4 (74.6)	87.3 (82.4)

[1]Based on 249 incident cases and 4,201 subcohort members. –[2]Based on 260 incident cases and 4,441 subcohort members.

Moreover, these factors are well-known risk factors of RCC and may be associated with a "healthy" lifestyle, which may also be associated with vegetable and fruit consumption. For all analyses on vegetable consumption, fruit consumption was also included as a confounder and vice versa. We investigated possible interaction by sex by entering an interaction term in the model and assessing the significance of this term using the Wald test. Since no interaction on RCC risk between sex and dietary intakes was observed, results are shown for men and women combined. Furthermore, total vegetable and fruit consumption, vegetable consumption, and fruit consumption are presented stratified by smoking status (never, ex- or current smoker), BMI (<25 kg/m^2 or ≥ 25 kg/m^2) and a history of hypertension (yes or no).

RRs and corresponding 95% confidence intervals (CI) for RCC were estimated using Cox proportional hazard models processed with the STATA statistical software package (STATA statistical software, Release 7, 2001; STATA Corporation, College Station, TX) after testing the proportional hazards assumption using scaled Schoenfeld residuals.[25] The proportional hazards assumption was not rejected. Standard errors were estimated using the robust Huber-White sandwich estimator to account for additional variance introduced by sampling from the cohort.[26] To obtain *p*-values for dose-response trends, ordinal exposure variables were fitted as continuous terms. Two sided *p*-values are reported throughout this article.

Results

The mean age (standard deviation) was 62.1 (3.9) for cases and 61.4 (4.2) for subcohort members. Sixty-five percent of cases were male compared to 49% of subcohort members. The mean BMI was somewhat higher for cases than for subcohort members (25.5 kg/m^2 compared to 25.1 kg/m^2). Almost a third (30%) of the cases and approximately a quarter (26%) of subcohort members reported a history of hypertension.

Also, cases were more often current smokers (38% compared to 29%) or ex-smokers (38% compared to 35%) and smoked more and longer than subcohort members (within the strata of ex- and current smokers).

No statistically significant interaction was shown for sex and total vegetable and fruit consumption (p-value = 0.40), for sex and vegetable consumption (p-value = 0.12) or for sex and fruit consumption (p-value = 0.99), so RRs for RCC were calculated for men and women combined.

Differences in vegetable consumption between cases and subcohort members were small (Table I). However, mean fruit consumption was somewhat lower for cases than for subcohort members, and this difference was present in all fruit groups (Table I).

TABLE II – MEAN DAILY VEGETABLE AND FRUIT CONSUMPTION AMONG RENAL CELL CARCINOMA (RCC) CASES AND SUBCOHORT MEMBERS AT BASELINE, ACCORDING TO CIGARETTE SMOKING (NEVER, EX- OR CURRENT SMOKER), BODY MASS INDEX (BMI; < 25 AND ≥25) AND HISTORY OF HYPERTENSION REPORTED (YES OR NO), NETHERLANDS COHORT STUDY ON DIET AND CANCER, 1986–1995

	Vegetable consumption				Fruit consumption			
	Cases (*n*)	Cases Mean (SD)	Subcohort members (*n*)	Subcohort Mean (SD)	Cases (*n*)	Cases Mean (SD)	Subcohort members (*n*)	Subcohort Mean (SD)
Never smoker	61	183.9 (71.4)	1,496	187.4 (74.6)	63	188.2 (113.6)	1,588	202.5 (123.3)
Ex-smoker	92	186.5 (73.4)	1,525	192.9 (74.5)	100	172.2 (106.3)	1,594	173.4 (117.1)
Current smoker	96	198.4 (82.8)	1,180	183.8 (78.2)	97	134.3 (112.5)	1,259	143.3 (108.7)
BMI < 25	119	187.3 (72.7)	2,221	188.3 (76.4)	124	151.4 (99.3)	2,344	175.9 (119.5)
BMI ≥ 25	130	193.4 (80.4)	1,980	188.4 (74.8)	136	171.5 (122.4)	2,097	174.5 (119.4)
No history of hypertension	172	187.7 (79.5)	3,118	186.9 (74.7)	180	161.0 (115.0)	3,290	181.3 (118.4)
History of hypertension	77	196.6 (70.0)	1,083	192.6 (78.3)	80	164.0 (106.5)	1,151	173.2 (119.7)

Table II shows means of vegetable and fruit consumption for never, ex- and current smokers, for a BMI <25 and ≥25 and for a positive history of hypertension or not (Table II). Similar means were observed for vegetable consumption in different smoking groups and for strata of BMI and a history of hypertension. Mean fruit consumption was higher in never smokers. In the stratum of current smokers, cases ate more vegetables and less fruit than subcohort members. Among never smokers, cases consumed less fruit than subcohort members (Table II). Fruit consumption was somewhat lower for cases with a BMI <25 (Table II).

Multivariable rate ratios of RCC for total vegetable and fruit consumption as well as for botanical groups of vegetable and fruit consumption are shown in Table III. We also analysed age- and sex-adjusted rates, but these were not very different (data not shown). "All vegetables and fruits," "all vegetables" and "all fruits" were not (inversely) associated with RCC risk (all RRs equalled 1). RRs of RCC for these groups hardly changed after exclusion of the first 2 years of follow-up (data not shown).

Legume consumption was associated with an increased risk for every 25 grams of legume consumed more per day (multivariable adjusted RR: 1.14; 95% CI 0.99–1.33) (Table III). This increased risk was restricted to the highest quintile of legume consumption (RR: 1.31; 95% CI 0.83–2.07). An increment of 25 grams per day of raw, leafy vegetables was associated with a reduced RCC risk (RR: 0.68; 95% CI 0.45–1.04), with an indication of a decreasing risk with increasing consumption (*p*-value for trend: 0.11) (Table III).

Table IV shows RRs of RCC for individual vegetables and fruits. No statistically significant reduced or increased risks were observed for individual vegetables. A significantly increased risk of RCC was observed for mandarin consumption (RR: 1.76; 95% CI 1.28–2.42). Other citrus fruits, however, were not associated with either an increased or decreased risk of RCC (Table IV). Banana consumption may be associated with a reduced RCC risk (RR: 0.85; 96% CI 0.72–1.01).

Table V shows multivariable-adjusted RRs for vegetable and fruit consumption, stratified by smoking status, BMI and history of hypertension. The estimated RRs did not differ largely between strata. None of the interaction terms of smoking, BMI or history of hypertension with tertiles of total vegetable consumption or with total fruit consumption were statistically significant.

Discussion

Neither total vegetable and/or fruit consumption, non-consumption of a botanical group of vegetables or fruits or individual vegetable or fruit consumption was associated with a decreased RCC risk in this cohort study. The only statistically significant result observed in 30 analyses of specific vegetables and fruits was an increased risk for mandarin consumption, which must be regarded cautiously because of multiple testing. Also, no modifying effect for smoking, BMI or a history of hypertension could be shown.

The prospective nature of a cohort study together with the completeness of follow-up, as has been achieved in our study, reduced the potential for selection bias to a minimum. Information bias, *i.e.,* a change in (report of) dietary habits of RCC cases due to the disease, is also largely avoided in a prospective study because dietary habits were reported before the disease was diagnosed. A change in dietary habits of subjects with preclinical RCC at the time of completing the baseline questionnaire remains possible. An indicator of advanced disease such as weight loss is estimated to be associated with RCC in approximately 35% of cases.[27] Weight loss may be induced by substances such as cytokines, insulin, inflammatory mediators, etc., produced in pathologic amounts by the tumour.[27] However, results excluding the first 2 years of follow-up did not differ from presented results (including the first 2 years of follow-up), indicating that our results were not influenced by the possible presence of preclinical RCC cases. Also, more than 50% of RCCs are now detected incidentally because of the more pervasive use of noninvasive imaging for the evaluation of a variety of nonspecific symptom complexes.[27]

Residual confounding by risk factors for RCC such as smoking or BMI is a realistic threat. Clustering of low vegetable and fruit consumption with smoking has been reported for the Dutch population,[28] and insufficient control of 1 factor will then confound the association between the other factor and RCC. We tried to model cigarette smoking habits such that they best explained RCC risk, resulting in a model including the habitual number of cigarettes smoked per day (smoking amount) and the number of years smoked (smoking duration), both as continuous variables. Furthermore, estimated RRs were not different for smoking strata (never, ex-, current).

Correction for BMI may have influenced results because high vegetable and fruit consumption might be associated with a lower BMI (as a result of the dietary pattern). However, the correlation of BMI with total vegetable and fruit consumption is not large ($r = 0.025$; p-value $= 0.0781$). Also, mean BMI did not differ for quintiles of total vegetable and fruit consumption, vegetable consumption, and fruit consumption (mean BMI range: 24.8–25.2 kg/m^2). Moreover, the RR and corresponding 95% CI for vegetable and fruit consumption did not change after removing BMI from the model.

Although we measured vegetable and fruit consumption extensively, a potential limitation remains misclassification of exposure. Usual vegetable consumption is not easy to assess in food-frequency questionnaires (or in other methods of dietary assessment), particularly if portion sizes have to be estimated. In the NLCS validation study, the FFQ was tested against 3-day diaries completed at 3 time points during a calendar year among 212 randomly selected subcohort members. The correlation coefficient for total vegetable consumption was 0.4,[23] which is moderate but comparable to the figure reported for many other prospective studies.[29,30] One of the reasons for the low correlation may be the relative lack of true contrast in the frequency of vegetable consumption in a

TABLE III – MULTIVARIABLE-ADJUSTED RATE RATIOS AND 95% CONFIDENCE INTERVALS (CI) FOR RENAL CELL CARCINOMA (RCC) FOR TOTAL AND SUBGROUPS OF VEGETABLE AND FRUIT CONSUMPTION, NETHERLANDS COHORT STUDY ON DIET AND CANCER, 1986–1995

Vegetable/fruit group	Quintile of consumption					*p*-value trend	Continuous/25g per day
	1 (low)[1]	2	3	4	5 (high)		
All vegetables and fruits							
Median consumption (g/day)	189	275	343	418	556		
Cases of RCC	50	34	48	51	39		222
Person-years	6,601	6,727	7,016	6,789	6,979		34,111
Multivariable-adjusted rate ratio (RR)[2]	1	0.69	0.94	1.01	0.78	0.79	1.00
95% CI	-	0.44–1.09	0.62–1.42	0.67–1.52	0.50–1.21		0.97–1.02
All vegetables							
Median consumption (g/day)	104	145	178	217	287		
Cases of RCC	48	44	38	50	42		222
Person-years	6,587	6,933	6,888	6,831	6,873		34,111
Multivariable-adjusted RR[2]	1	0.87	0.77	1.04	0.84	0.76	1.00
95% CI	-	0.57–1.34	0.49–1.19	0.68–1.59	0.54–1.31		0.96–1.06
Cooked vegetables[3]							
Median consumption (g/day)	79	114	142	173	230		
Cases of RCC	48	40	42	42	50		222
Person-years	6,622	6,802	7,012	6,848	6,827		34,111
Multivariable-adjusted RR[2]	1	0.79	0.78	0.81	0.97	0.24	1.01
95% CI	-	0.51–1.23	0.51–1.21	0.53–1.25	0.63–1.48		0.95–1.07
Raw vegetables[3]							
Median consumption (g/day)	8	22	34	48	76		
Cases of RCC	33	47	50	52	40		222
Person-years	6,753	6,802	6,770	6,905	6,881		34,111
Multivariable-adjusted RR[2]	1	1.46	1.64	1.63	1.26	0.88	0.99
95% CI	-	0.91–2.33	1.04–2.59	1.04–2.58	0.78–2.06		0.89–1.09
Legumes[4]							
Median consumption (g/day)	10	19	28	38	60		
Cases of RCC	44	39	41	40	58		222
Person-years	6,586	6,976	6,761	6,898	6,890		34,111
Multivariable-adjusted RR[2]	1	0.86	0.92	0.91	1.31	0.27	1.14
95% CI	-	0.54–1.38	0.58–1.46	0.56–1.49	0.83–2.07		0.99–1.33
Brassicas[4]							
Median consumption (g/day)	10	20	28	38	57		
Cases of RCC	43	34	51	52	42		222
Person-years	6,627	6,819	6,915	6,847	6,904		34,111
Multivariable-adjusted RR[2]	1	0.78	1.12	1.18	0.90	0.81	0.98
95% CI	-	0.49–1.26	0.72–1.73	0.74–1.88	0.54–1.50		0.80–1.20
Leafy vegetables, cooked[4]							
Median consumption (g/day)	4	12	19	27	41		
Cases of RCC	41	48	46	41	46		222
Person-years	6,763	6,861	6,835	6,806	6,847		34,111
Multivariable-adjusted RR[2]	1	1.17	1.15	1.01	1.10	0.98	0.94
95% CI	-	0.74–1.83	0.72–1.82	0.61–1.65	0.67–1.80		0.75–1.19
Leafy vegetables, raw[4]							
Median consumption (g/day)	2	4	7	12	22		
Cases of RCC	54	45	42	43	38		222
Person-years	7,836	5,759	6,876	6,736	6,905		34,111
Multivariable-adjusted RR[2]	1	1.04	0.83	0.84	0.71	0.11	0.68
95% CI	-	0.68–1.60	0.54–1.29	0.54–1.30	0.45–1.11		0.45–1.04
Allium vegetables, cooked[4]							
Median consumption (g/day)	5	16	24	37	60		
Cases of RCC	65	31	45	38	43		222
Person-years	9,447	4,187	6,939	6,797	6,742		34,111
Multivariable-adjusted RR[2]	1	1.18	0.90	0.74	0.84	0.16	1.01
95% CI	-	0.75–1.85	0.60–1.36	0.48–1.14	0.55–1.30		0.87–1.17
All fruits							
Median consumption (g/day)	44	107	155	215	326		
Cases of RCC	47	45	51	39	50		232
Person-years	6,985	7,156	7,156	7,377	7,346		36,021
Multivariable-adjusted RR[2]	1	0.98	1.15	0.84	1.08	0.58	1.00
95% CI	-	0.64–1.50	0.76–1.74	0.54–1.30	0.71–1.66		0.97–1.03
Citrus fruit[5]							
Median consumption (g/day)	3	26	60	98	176		
Cases of RCC	43	40	63	35	51		232
Person-years	7,092	7,275	7,206	7,195	7,253		36,021
Multivariable-adjusted RR[2]	1	0.94	1.48	0.84	1.22	0.51	1.01
95% CI	-	0.60–1.47	0.98–2.26	0.52–1.36	0.79–1.89		0.97–1.06
Apples and pears[5]							
Median consumption (g/day)	6	40	80	116	181		
Cases of RCC	45	42	59	42	44		232
Person-years	7,151	7,154	7,375	6,995	7,346		36,021
Multivariable-adjusted RR[2]	1	0.97	1.37	1.06	1.04	0.71	1.00
95% CI	-	0.63–1.51	0.91–2.06	0.67–1.67	0.67–1.62		0.96–1.04

[1]Reference category.–[2]Multivariable models include adjustment for age, sex, current smoker (yes/no), number of cigarettes per day, number of smoking years, body mass index (BMI) history of hypertension and fruit or vegetable consumption for vegetable or fruit consumption, respectively.–[3]Cooked and raw vegetables are simultaneously entered in the model. –[4]Legumes, brassicas, cooked leafy vegetables, raw leafy vegetables, allium vegetables, carrots, beets, tomatoes and other cooked and raw vegetables are simultaneously entered in the model.–[5]Citrus fruit, apples and pears, grapes, bananas, strawberries and other fruits and fruit juices are simultaneously entered in the model.

TABLE IV – RATE RATIOS AND 95% CONFIDENCE INTERVALS (CI) FOR RENAL CELL CARCINOMA (RCC) FOR INDIVIDUAL VEGETABLE AND FRUIT CONSUMPTION, NETHERLANDS COHORT STUDY ON DIET AND CANCER, 1986–1995

Variable[1]	Median consumption (grams/day)	Age, and sex-adjusted rate ratio (RR) per 25 g increment	95% CI	Multivariable-adjusted RR[2] per 25 g increment	95% CI
Brussels sprouts	7	1.16	0.77–1.77	1.03	0.65–1.65
Leek	6	0.94	0.64–1.37	0.92	0.61–1.40
Sauerkraut	5	1.46	0.75–2.84	1.72	0.86–3.44
Cauliflower	12	0.93	0.64–1.36	0.89	0.60–1.32
Cabbage	5	0.81	0.50–1.33	0.87	0.51–1.47
Spinach	8	0.80	0.53–1.20	0.79	0.51–1.22
Endive, prepared	10	1.21	0.90–1.63	1.07	0.78–1.47
Red beets	6	0.84	0.53–1.32	0.95	0.60–1.49
Carrots, prepared	7	0.98	0.65–1.47	0.92	0.60–1.43
String and sliced beans	17	1.16	0.94–1.43	1.17	0.94–1.46
Broad beans	1	1.20	0.78–1.87	1.06	0.66–1.68
Kale	2	1.63	0.64–4.12	1.74	0.66–4.61
Endive, raw	0	0.60	0.25–1.43	0.63	0.25–1.60
Lettuce	6	0.82	0.50–1.33	0.77	0.46–1.30
Carrots, raw	0	0.89	0.60–1.31	0.93	0.61–1.41
Rhubarb	0	1.03	0.50–2.12	1.09	0.52–2.28
Applesauce	4	0.98	0.79–1.22	0.98	0.78–1.24
Onions	11	1.11	0.92–1.33	1.08	0.88–1.32
Tomatoes	19	1.13	0.99–1.29	1.11	0.97–1.28
Mushrooms	4	0.82	0.32–2.08	0.82	0.29–2.34
Sweet peppers	1	0.58	0.22–1.54	0.72	0.28–1.87
Gherkins	0	0.76	0.49–1.18	0.71	0.42–1.21
Raisins	0	0.34	0.04–2.58	0.43	0.05–3.35
Mandarins	2	1.77	1.31–2.40	1.76	1.28–2.42
Oranges	32	1.00	0.95–1.06	1.02	0.96–1.08
Grapefruit	0	0.96	0.83–1.12	0.97	0.83–1.14
Grapes	1	0.77	0.53–1.12	0.73	0.49–1.09
Bananas	4	0.87	0.75–1.01	0.85	0.72–1.01
Apples, pears	53	0.99	0.95–1.03	1.00	0.96–1.04
Strawberries	5	0.88	0.57–1.37	0.99	0.65–1.50

[1]All vegetables variables (Brussels sprouts through gherkins) are entered simultaneously in the model; rate ratios are based on 249 cases and 36,886 person-years. All fruit variables (raisins through strawberries) are entered simultaneously in the model; rate ratios are based on 260 cases and 38,994 person-years. The number of cases and person-years in the subcohort is lower in multivariable analyses due to missing values.–[2]Multivariable models include adjustment for age, sex, current smoker (yes/no), number of cigarettes per day, number of smoking years, body mass index (BMI), history of hypertension and fruit or vegetable consumption for vegetable for fruit consumption, respectively.

TABLE V – RATE RATIOS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR RENAL CELL CARCINOMA (RCC) FOR VEGETABLE AND FRUIT CONSUMPTION, ACCORDING TO CIGARETTE SMOKING (NEVER, EX- OR CURRENT SMOKER), BODY MASS INDEX (BMI; <25 AND ≥25) AND HISTORY OF HYPERTENSION REPORTED (YES OR NO), NETHERLANDS COHORT STUDY ON DIET AND CANCER, 1986–1995

	No. of cases person-years in subcohort	Tertile of vegetable and fruit consumption			*p*-value trend	Continuous per 25 g increment
		1 (low)	2	3 (high)		
Vegetable consumption						
Never smoker[1]	59/12,970	1 (reference)	0.92 (0.47–1.77)	1.11 (0.57–2.18)	0.77	0.99 (0.91–1.09)
Ex-smoker[2]	82/12,221	1 (reference)	0.91 (0.52–1.59)	0.84 (0.48–1.49)	0.56	0.96 (0.87–1.05)
Current smoker[2]	81/8,921	1 (reference)	0.95 (0.53–1.71)	1.24 (0.72–2.15)	0.44	1.05 (0.98–1.13)
BMI <25[3]	112/18,673	1 (reference)	0.84 (0.52–1.36)	1.08 (0.67–1.73)	0.77	1.00 (0.94–1.07)
BMI ≥25[3]	117/16,564	1 (reference)	1.00 (0.63–1.59)	1.04 (0.65–1.66)	0.87	1.01 (0.94–1.08)
No history of hypertension[4]	151/25,241	1 (reference)	0.86 (0.57–1.31)	1.01 (0.67–1.51)	0.98	1.00 (0.94–1.06)
History of hypertension[4]	71/8,870	1 (reference)	1.02 (0.54–1.92)	1.07 (0.56–2.04)	0.83	1.01 (0.93–1.08)
Fruit consumption						
Never smoker[1]	61/13,755	1 (reference)	0.76 (0.40–1.41)	0.71 (0.38–1.33)	0.30	0.98 (0.93–1.04)
Ex-smoker[2]	90/12,734	1 (reference)	0.94 (0.54–1.63)	1.21 (0.71–2.06)	0.46	1.01 (0.97–1.05)
Current smoker[2]	81/9,532	1 (reference)	1.17 (0.69–1.99)	0.79 (0.43–1.46)	0.54	0.99 (0.93–1.05)
BMI <25[3]	117/19,698	1 (reference)	0.97 (0.61–1.53)	0.81 (0.50–1.31)	0.39	0.97 (0.93–1.01)
BMI ≥25[3]	122/17,627	1 (reference)	0.85 (0.53–1.34)	0.95 (0.60–1.49)	0.82	1.01 (0.97–1.06)
No history of hypertension[4]	159/26,597	1 (reference)	1.04 (0.70–1.55)	0.96 (0.63–1.44)	0.83	1.01 (0.97–1.04)
History of hypertension[4]	73/9,423	1 (reference)	0.81 (0.44–1.46)	0.88 (0.49–1.57)	0.67	0.98 (0.93–1.03)

[1]Rate ratios are adjusted for age, sex, BMI, history of hypertension and fruit or vegetable consumption for vegetable or fruit consumption, respectively.–[2]Rate ratios are adjusted for age, sex, number of cigarettes smoked per day, years of cigarette smoking, BMI, history of hypertension and fruit or vegetable consumption for vegetable or fruit consumption, respectively.–[3]Rate ratios are adjusted for age, sex, current smoker (yes/no), number of cigarettes smoked per day, years of cigarette smoking, history of hypertension and fruit or vegetable consumption for vegetable or fruit consumption, respectively.–[4]Rate ratios are adjusted for age, sex, current smoker (yes/no), number of cigarettes smoked per day, years of cigarette smoking, BMI and fruit or vegetable consumption for vegetable or fruit consumption, respectively.

population such as the Dutch, because people are accustomed to a diet including only 1 hot meal per day, which almost always includes vegetables. This relative lack of contrast and thus a relatively large measurement error may result in attenuation of the estimated RR for the association of total vegetable consumption and RCC. Due to individual preferences, contrast in consumption frequency of specific vegetables is much higher, which means that attenuation is probably less important for RRs estimated for specific vegetables. It was not possible to assess validity for specific vegetables in the NLCS validation study because 9 days of dietary record (3-day diaries completed at 3 time points during a calendar year) are not sufficient to estimate consumption frequency of specific vegetables. To minimize the amount of uninformative data in addition to the general dietary exclusion criteria, we excluded subjects who appeared not to have understood how to fill out the questions on vegetable consumption, which occurred in the first part of the food-frequency questionnaire; an extreme score on the vegetable error index defined those subjects. For the same cohort, statistically significant inverse associations have been described between most categories of vegetable or fruit consumption and lung cancer[24] as well as between brassica vegetables and cooked leafy vegetables and colon cancer,[31] indicating that measurement error or too little contrast most likely do not mask a possible association.

To our knowledge, only 3 cohort studies[11,14,16] have evaluated the relationship between vegetable and/or fruit consumption and RCC. The Iowa Women's Health Study with data on 124 women reported no association for "total fruit and vegetables" and for "cruciferous or green leafy vegetables".[16] In an earlier report from this study on 62 cases, a null association was reported for consumption of "fruit + vegetables," "fruit" and "vegetables" and RCC risk.[32] These results were confirmed in our study.

The Swedish Mammography Cohort included 122 Swedish women and observed a nonsignificant inverse association between the combined consumption of total fruits and total vegetables and RCC risk. Individual vegetables were associated with nonsignificantly decreased risks, except for root vegetables, which were statistically significantly inversely associated. For individual fruits, a nonsignificant inverse association with apples, a null association with citrus fruit, a statistically significant inverse association with banana and a nonsignificant increased risk with fruit juice consumption were observed.[11] The only agreement with the current study was the protective effect for banana consumption. A direct relationship between total phenolic content and total antioxidant activity in phytochemical extracts of different fruits has been observed; bananas ranked 6th of 11 fruits tested.[33] Bananas had the highest bound-W phenolics content, but the significance of bound phytochemicals in fruits to human health is not clear.[33] The other cohort study was conducted amongst Californian Seventh-Day Adventists with 8 male and 6 female incident cases.[14] Participants in this study seldom smoked (only 3% current smokers and 20% ex-smokers) and were mostly vegetarian. This study only reported on green salad and fruit consumption for which a statistically nonsignificant inverse association was found.

Ten case-control studies[6–10,12,13,15,17,18] have evaluated the relationship between vegetable and/or fruit consumption and RCC risk. Three studies are based on a large number of cases and population-based controls. The first was conducted in Los Angeles and reported on dark green vegetables, yellow-orange vegetables, tomatoes or tomato products, citrus fruits and citrus fruit juices in relation to RCC, based on 1,204 RCC cases and an equal number of neighbourhood controls matched by sex, date of birth (within 5 years) and ethnicity.[8] Only dark green vegetables showed a significant inverse association with RCC risk. Results were not different for smokers or never smokers, for persons with a BMI greater or less than 24.4 kg/m^2 or for persons with or without a history of hypertension, which was confirmed in this study. The second study was performed in Canada among 1,279 incident cases and 5,370 controls. A significant inverse association with RCC was observed with increasing total consumption of vegetables and vegetable juices for males and females combined. Statistically significant inverse associations between total consumption of dark green vegetables (broccoli and spinach) and cruciferous vegetables (broccoli, cabbage, cauliflower and Brussels sprouts) were observed for females only. Smoking did not modify the association between vegetable and fruit consumption and RCC.[9] The other large case-control study was a multicenter study from Australia, Denmark, Sweden and the United States (International renal-cell cancer study)[15] and investigated total vegetables, orange/dark green vegetables, cruciferous vegetables, allium vegetables, total fruit, citrus, and apples and pears among 1,185 cases and 1,526 controls. A significantly decreased risk in quartile 4 for orange/dark green vegetables was observed, with most estimates less than, but close to one and a more pronounced statistically significant inverse association with RCC in never smokers. Four of the case-control studies, referred to earlier, were part of the International Renal Cell Cancer Study.[12,13,17,18] These studies reported a statistically significant inverse association with RCC for fruit consumption[12,13] and null associations.[16–18] However, results from one study were not included in the aggregated article because other methods were used for dietary assessment,[13] whereas another article included a larger case group,[18] and a third article also reported on food intake 20 years before the interview (with similar results).[12] Data from case-control studies from Italy, Germany and China mostly showed decreased risks with vegetable and fruit consumption.[6,7,10,13] Statistically significant decreased associations were only observed for carrot consumption,[10] the highest tertile of green vegetable consumption,[6] total vegetable and total fruit consumption but confined to men[7] and the highest tertile of fruit consumption.[6,13] None of the earlier mentioned studies reported on mandarin consumption, which suggests this was either not investigated or that no statistically significant association was observed.

We were able to assess the independent association with specific vegetable and fruit groups and for individual vegetables and fruits by adjusting for total vegetable and/or fruit consumption. Only one cohort study[11] and one hospital-based case-control study also adjusted for total vegetable/fruit consumption.[6] All significantly reduced risks reported so far seem to be confined to a subgroup such as one specific type of vegetable or fruit or to a specific tertile quartile or quintile, which may suggest chance results due to multiple testing. In our study, statistically significant results for a quintile were also incidentally observed, but we did not observe this in multivariable-adjusted analyses based on the continuous vegetable or fruit variable or in the trend over the categories.

To our knowledge, this is the largest prospective study on vegetable and fruit consumption and RCC risk currently available. Our results suggest the absence of an association between vegetable and fruit consumption and RCC risk.

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Appendix

TABLE I – COMPOSITION OF BOTANICAL VEGETABLE AND FRUIT GROUPS

Group name	Vegetables or fruit represented in this group
Cooked vegetables	Endive (prepared); cauliflower (prepared); kale (prepared); mushrooms; leek (prepared); spinach (prepared); Brussels sprouts (prepared); onion (prepared); carrots (prepared); sauerkraut; beets (prepared); broad beans (prepared); cabbage (prepared); sliced beans, string beans (prepared); sweet peppers; other vegetables prepared
Raw vegetables	Raw endive; lettuce; carrots (raw); tomatoes; other raw vegetables
Legumes	Broad beans (prepared); pulses; sliced beans, string beans (prepared)
Brassicas	Cauliflower (prepared), cabbage (prepared), kale (prepared); Brussels sprouts (prepared)
Leafy vegetables, cooked	Endive (prepared); spinach (prepared)
Leafy vegetables, raw	Raw endive; Lettuce; Cress[1]
Allium vegetables	Leek (prepared); onions (prepared); cocktail onions (sweet-sour),[1]Garlic[2]
Carrots	Carrots (prepared); canned carrots[1]
Beets	Beets (prepared); beet juice
Tomatoes	Tomatoes (raw); tomato juice
Other cooked vegetables	Other vegetables prepared[1]
Other raw vegetables	Other raw vegetables[1]
Citrus fruit	Lemons,[1] fresh lemon juice,[1] grapefruit, fresh grapefruit juice; mandarins; oranges, fresh orange juice
Grapes	Grapes (blue and white)
Bananas	Bananas
Apples/pears	Applesauce; apples, pears
Strawberries	Strawberries
Other fruit and fruit juices	Other fruits and fruit juices[1]

[1]Vegetable or fruit not specifically asked about in the questionnaire but entered in the open-ended question where participants could fill out other foods regularly eaten.–[2]Data derived from question on supplement use.